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Complete if Known Substitute for form 1449A/PTO Application Number 10/054712 INFORMATION DISCLOSURE Filing Date November 13, 2001 Gerald R. Crabtree RECEIVED STATEMENT BY APPLICANT First Named Inventor 2122 1634 Art Unit (use as many sheets as necessary) Not Yet Assigned D Examiner Name Technology Center 2100 APBI-P08-317 Attorney Docket Number Sheet 1 of 11

Γ			U.S.	PATENT DO	CUMENTS			
F	Cite	Document Number	Publication D	Name of Retenter	me of Patentee or Applicant	Pages, Columns, Lices, Where Relevant		
Examiner Cite Initiats* No.		Number-Kind Code ² (if known)		MM-DD-YYYY of Cited Document		Passages or Relevant		EIVED
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21	AB	6,054,436	04-25-20	00	Crabtree et al.	MA	Y	
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01	AC	EP 0 594 847		05-04-1994	Tonen Corp.		T	
21	AD	WO 92/01052		01-23-1992	Tonen Corp.			}
Do	AE	WO 93/23550		11-25-1993	Genentech, Inc.			
24 24 21	AF	WO 93/25533	3	12-23-1993	Abbott Labs			

^{*}EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant

¹ Applicant's unique citation designation number (optional). ² See attached Kinds Codes of USPTO Patent Documents at www.uspto.gog/ or MPEP 901.04. ³
Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the application number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 18 if possible. ⁴ Applicant is to place a check mark here if English language Translation is attached.

		OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	ler Cite Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the titem (book, magazine, journal, serial, sympostum, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published,				
DJ	AG	Alberg, D.G and Schreiber, S.L. Structure-Based Design of a Cyclophilin-Calcineurin Bridging Ligand. Science 262, 248-250 (1993).			
y	AH	Albers, M.W. et al. Substrate Specificity for the Human Rotamase FKBP: A View of FK506 and Rapamycin as Leucine (twisted amide)-Proline Mimics. <i>J. Org. Chem.</i> 55, 4984-4986 (1990).			
21	Al	Albers, M.W. et al. Relationship of FKBP to PKCI-1. Nature 351, 527 (1991).			
AL	AJ	Albers, M.W. et al. FKBP, Thought to be Identical to PKCI-2, Does Not Inhibit Protein Kinase C. BloMed. Chem. Lett. 1, 205-210 (1991).			
by.	AK	Albers, M.W. et al. An FKBP-Rapamycin Sensitive, Cyclin-Dependent Kinase Activity That Correlates with the FKBP Rapamycin-Induced G1 Arrest Point in MG-63 Cells. <i>Annals of N. Y. Aced. Sci.</i> 696, 54-62 (1993).			
DJ	AL	Andrus, M.B. and Schreiber, S.L. Structure-Based Design of an Acyclic Ligand That Bridges FKBP12 and Calcineurin. J. Am. Chem. Soc. 115, 10420-10421 (1993).			
DJ	AM	Ben-Levy, R. et al. A oncogenic point mutation confers High Affinity Ligand Binding to the neu Receptor. J. Biol. Chem. 267, 17304-17313 (1992).			

Examiner Signature	Durid	fambertum.	Date Considered	11/11/03

PTO/SB/08A (10-01)
Approved for use through 10/31/2002-0MB 0851-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE and to a collection of information unless it contains a valid OMB control number.

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Sheet	2	of	11	Attorney Docket Number	APBI-P08-317	hter 2100	
					46CUIIOIOBY C	ico.	

M	AN	Bergsma, D.J. et al. The Cyclophilin Multigene Family of Peptidyl-Prolyl Isomerases. J. Biol. Chem. 266, 23204-23214 (1991).	PAC
DJ.	OA	Bernard, O. et al. High-affinity Interleukin-2 Binding by an Oncogenic Hybrid Interleukin-2 Epidermal Growth Factor Receptor Molecule. <i>PNAS</i> 84, 2125-2129 (1987).	PECE/V MAY 2 3 200. DENVEO 1500/28
M	AP	Bierer, B.E. et al. Mechanisms of Immunosuppression by FK506: Preservation of T Cell Transmembrane Signal Transduction. <i>Transplantation</i> 49, 1168-1202 (1990).	EN 50 1500
DL.	AQ	Bierer, B.E. et al. Probing Immunosuppressant Action with a Nonnatural Immunosuppressive Ligand. Science 250, 556-559 (26 Oct. 1990).	000/28
D1	AR	Bierer, B.E. et al. Two Distinct Signal Transmission Pathways in T Lymphocytes are Inhibited by Complexes Formed Between an Immunophilin and Either FK506 or Rapamycin. <i>PNAS</i> 87, 9231-9235 (Dec. 1990).	
21	AS	Bierer, B.E. et al. The Effect of the Immunosuppressant FK506 on Alternate Pathways of T Cell Activation. Eur. J. Immunol. 21, 439-445 (1991).	
DL	ΑT	Bonnerot, C. et al. Role of associated γ-chain in Tyrosine Kinase Activation via Murine FcRIII. EMBO J. 11, 2747-2757 (1992).	
21	ΑÚ	Bram, R.J. et al. Identification of the Immunophilins Capable of Mediating Inhibition of Signal Transduction by Cyclosporin A and FK506: Roles of Calcineurin Binding and Cellular Location. <i>Mol. Cell. Biol.</i> 13, 4760-4769 (Aug. 1993).	
31	AV	Byrn, R.A. et al. Biological Properties of a CD4 Immunoadhesin. Nature 344, 667-670 (12 April 1990).	
Ðſ	AW	Cantley, L.C. et al. Oncogenes and signal transduction. Cell 64, 281-302 (25 Jan. 1991).	
DJ	AX	Chan, A.C. et al. The ζ Chain is associated with a Tyrosine Kinase and upon T-Cell Antigen Receptor Stimulation Associates with ZAP-70, a 70-kDa Tyrosine Phosphoprotein. <i>PNAS</i> 88, 9166-9170 (Oct. 1991).	
M	ΑÝ	Chung, J. et al. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. <i>Cell</i> 69, 1227-1236 (26 June 1992).	
31	ΑŻ	Clark, M.R. et al. The B Cell Antigen Receptor Complex: Association of $\lg_{-\alpha}$ and $\lg_{-\beta}$ with Distinct Cytoplasmic Effectors. Science 258, 123-128 (2 Oct. 1992).	
91	BA	Clipstone, N.A. et al. Calcineurin: Molecular analysis of its interaction with drug-immunophilin complexes and its role in the regulation of NF-AT. <i>J. Cell. Biochem. Suppl.</i> 0 (18B) 274, Abstract #I410 (1994).	
91	BB	Crabtree, G. R. IL-2 receptor in the pathogenesis of human lymphoma. Abstract of NIH Grant 5R01CA039612-03 (1987).	
21	BC	Crabtree, G. R. Pathways of T lymphocyte activation. Abstract of NIH Grant 2R01CA039612-07 (1991).	
xaminer	1	and fambuten Date Considered 11/11/03	

PTO/SB/08A (10-01)

Approved for use through 10/31/2002 OMB 0651-0031

U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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Substitute for form 1449A/PTO Complete If Known 10/054712 Application Number INFORMATION DISCLOSURE Filing Date November 13, 2001 STATEMENT BY APPLICANT First Named Inventor Gerald R. Crabtree 2122-1636 Art Unit (use as many sheets as necessary) Examiner Name Not Yet Assigned D. L Technology Denter 2100 Sheet 3 of 11 Attorney Docket Number APBI-P08-317

		IData /		
Dy	BS	Flanagan, W.M. et al. Nuclear association of a transcription factor essential for T cell activation by cyclosporin A and FK506. <i>J. Cell. Biochem. Suppl.</i> 0 (16 Part B), 237, Abstract #H514 (1992).		
DJ	BR	Flanagan, W.M. et al. Intracellular signal transmission: a novel role for the prolyl isomerases. J. Cell. Biochem. Suppl. 0 (16 Part A) 61, Abstract #B005 (1992).		
# <u></u>	BQ	Flanagan, W.M. et al. Nuclear Association of a T-Cell Transcription Factor Blocked by a Tyrosine Factor Blocked by FK-506 and Cyclosporin A. <i>Nature</i> 352, 803-807 (29 Aug. 1991).		
DJ_	BP	Fisher, M.J. et al. On the Remarkable Propensity for Carbon-Carbon Bond Cleavage Reactions in the C8-C10 Region of FK-506. <i>J. Org. Chem.</i> 56, 2900-2907 (1991).		
DI	ВО	Fischer, G. et al. Mip protein of Legionella pneumophila exhibits peptidyl-prolyl-cis/trans isomerase (Pplase) activity. <i>Mol. Microbiol.</i> 6, 1375-1383 (1992).		
쥐	BN	Fields, S. & Song, O-k A Novel Genetic System to Detect Protein-Protein Interactions. Nature 340, 245-246 (20 July 1989).		
AJ.	ВМ	Evans et al. Mechanistic study of the rhodium(I)-catalyzed hydroboration reaction. J. Am. Chem. Soc. 114, 6679-6685 (1992).		
AJ.	BL	Evans, D.A. et al. Mechanistic Study of the Rhodium(I)- and Iridium(I)- Catalyzed Hydroboration Reactions: Scope and Synthetic Applications. J. Am. Chem. Soc. 114, 6671-6679 (1992).		
M	вк	Engel, I. et al. High-Efficiency Expression and Solubization of Functional T-Cell antigen Receptor Heterodimers. Science 256, 1318-1321 (29 May 1992).		
A	BJ	Emmel, E.A. et al. Cyclosporin A Specifically Inhibits Function of Nuclear Proteins Involved in T-Cell Activation. <i>Science</i> 246, 1617-1620 (22 Dec. 1989).		
21	ВІ	Eiseman, E. and Bolen, J.B. Signal Transduction by the Cytoplasmic Domains of Fc∈RI-y and TCR0J-y in Rat Basophilic Leukemia Cells. <i>J. Biol. Chem.</i> 267, 21027-21032 (15 Oct. 1992).		
21	вн	Edalji, R. et al. High-Level Expression of Recombinant Human FK-Binding Protein from a Fusion Precursor. J. Prot. Chem. 11, 213-223 (1992).		900
DI	BG	Eberle, M.K. and Nuninger, F. Synthesis of the Main Metabolite (OL-17) of Cyclosporin A. J. Org. Chem. 57, 2689-2691 (1992).		1500/2900
21	BF	DiLella, A.G. et al. Chromosomal Band Assignments of the Genes Encoding Human FKBP12 and FKBP13. Biochem. Biophys. Res. Commun. 189, 819-823 (15 Dec. 1992). Donald, D.K. et al. C10 N-Acyl Modified FK-506: A Possible Hybrid Analogue of the Transition State of Petidyl-Prolyl Cis-Trans Isomerization. Tetrahedron Letters 31, 1375-1378 (1991). Durand, D.B et al. Characterization of Antigen Receptor Response Elements within the Interleukin-2 Enhancer. Mol. Cell. Biol. 8, 1715-1724 (April 1988). Eberle, M.K. and Nuninger, F. Synthesis of the Main Metabolite (OL-17) of Cyclosporin A. J. Org. Chem. 57, 2689-2691 (1992). Edalji, R. et al. High-Level Expression of Recombinant Human FK-Binding Protein from a Eusion Procursor. J. Prot. Chem. 11, 213-223 (1992).	AY W	232002
21	BE	Donald, D.K. et al. C10 N-Acyl Modified FK-506: A Possible Hybrid Analogue of the Transition State of Petidyl-Prolyl Cis-Trans Isomerization. <i>Tetrahedron Letters</i> 31, 1375-1378 (1991).	E	CEUC
2	BD	DiLella, A.G. et al. Chromosomal Band Assignments of the Genes Encoding Human FKBP12 and FKBP13. Biochem. Biophys. Res. Commun. 189, 819-823 (15 Dec. 1992).		

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PTO/SB/08A (10-01)
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eet		4	of	11	Attorney Docket Number	APBI-P08-317	
						APBI-P08-317	gy c
1	ВТ			al. Inhibition of Live 3, 496-498 (1992).	er, Kidney, and Intestine	Regeneration by Rapamycin.	
ᆚ	BU	113, 1409-1	411 (1991).		nunophilins). J. Am. Chem. Soc.	
り	BV	Revealed by One in the A	y Affin Absen	nity for a New Cydo ice of CsA. Cell 66,	philin: One in the Preser 799-806 (23 Aug. 1991)	•	1
D)	BW	Fuh, G. et a Science 256	l. Rat 5, 167	tional design of pote 7-1680 (19 June 19	ent antagonists to the hu 192).	man growth hormone receptor,	Co
メ	BX	Galat, A. et (1992).	al. A	Rapamycin-Selecti	ve 25 kDa Immunophilin	Biochemistry 31, 2427-2434	Ce
91	BY	of Amines.	Tetra	ahedron Letters 33,	2781-2784 (1992).	tongorit for / intoxy car borry action	
71	BZ	is Important	for is			d Portion of the Insulin Receptor Biochem. Biophys. Res. Comm.	
XL	CA	Haendler, B (1987).	et al.	. Complementary [NA for human T-cell cyc	clophilin. <i>EMBO J</i> . 6, 947-950	
DL.	СВ			. Yeast cyclophilin: 39-46 (1989).	isolation and characteriz	ation of the protein, cDNA and	
1	ÇC	Prolyl Isome	rase.	Nature 341, 758-7	60 (1989).	FK506 is a cis-trans Peptidyl-	
Y_	CD	Kinase. J. E	Biol. C	Chem. 266, 19908-1	9916 (1991).	Human c-kit Receptor Tyrosine	
¥1.	CE			il. The CD3CCytopl: 139-145 (1992).	asmic Domain Mediates	CD2-Induced T Cell Activation.	
<u></u>	CF				ds Demonstrate Commo	on Features of Signal	

21	CI	likeda, Y. et al. Structural Basis for Peptidomim 116, 4143-4144 (1994).	icry by a Natural Product.	. Am. Chem. Soc.
Examiner Signature		and lambuter	Date Considered	11/11/03

Transduction Leading to Exocytosis or Transcription. PNAS 88, 6229-6233 (July 1991).

Hultsch, T. et al. Inhibition of IgE Receptor-Mediated Exocytosis from Rat Basophilic Leukemia Cells by FK506 is Reversed by Rapamycin: Evidence for Common Signaling Pathways in Mast Cells and T Lymphocytes. FASEB J. 5, A1008 [3705] (1991).

Hung, D.T. & Schreiber, S.L. CDNA Cloning of a Human 25 kDa FK506 and Rapamycin Binding Protein. *Biochem. Biophys. Res. Comm.* 184, 733 (30 April 1992).

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PTO/SB/08A (10-01)
Approved for use through 10/31/2002.OMB 0851-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number. Complete if Known Substitute for form 1449A/PTO 10/054712 Application Number RECEIVED INFORMATION DISCLOSURE Filing Date November 13, 2001 STATEMENT BY APPLICANT First Named Inventor Gerald R. Crabtree MAY 2 0 2003 2122-1636 Art Unit (use as many sheets as necessary) APBI-P08-317 Technology Center 2100 Examiner Name Sheet 5 of 11 Attorney Docket Number

4		140 (1450).		
7.	СХ	Larson & Nuss. Cyclophilin-dependent stimulation of transcription by cyclosporin A. PNAS 90, 148 (1993).		
DI	CW	Lanier et al. Co-association of CD3c with a Receptor (CD16) for IgG Fc on Human Natural Killer Cells. Nature 342, 803-805 (1989).		
DI	CV	Lane et al. Complete Amino Acid Sequence of the FK506 and Rapamycin Binding Protein, FKBP, Isolated from Calf Thymus. J. Prot. Chem. 10, 151-160 (1991).		
DI	CÜ	Lammers et al. Differential Signaling Potential in Insulin- and IGF-1-receptor Cytoplasmic Domains. EMBO J. 8, 1369-1375 (1989).		
DJ	CT	Kruskal, B.A. et al. Phagocytic Chimeric Receptors Require Both Transmembrane and Cytoplasmic Domains from the Mannos Receptor. <i>J. Exp. Med.</i> 176, 1673-1680 (1992).		
A	CS	Krishnamurthy, S. Lithium Tris[(3-ethyl-3-pentyl)oxy]aluminum Hydride. A New Remarkably Chemoselective Reagent for the Reduction of Aldehydes in the Presence of Ketones. <i>J. Org. Chem.</i> 46, 4628-4629 (1981).		
A	CR	Kinet, JP. Antibody-Cell Interactions: Fc Receptors. Cell 57, 351-354 (5 May 1989).		
A	CQ	Ke, H. et al. Crystal Structures of Cyclophilin A Complexed with Cyclosporin A and N-methyl-4-[(E)-2-Butenyl]-4,4-Dimthyltheonine Cyclosporin A. Structure 2, 33-44 (15 Jan. 1994).		
Ŋ	СР	Kaye, R.E. et al. Effects of Cyclosporin A and FK506 on Fce Receptor type I-Initiated Increases in Cytokine mRNA in Mouse Bone Marrow-Derived Progenito Mast Cells: Resistance to FK506 is Associated with a Deficiency in FKBP12. PNAS 89, 8542-8546 (Sept. 1992).		
ĐJ		(16 Part B), 239, Abstract #H523 (1992).		~ <i>~0</i>
31	CN	Jin, YJ. et al. Molecular cloning of a membrane-associated human FK506- and rapamycin-binding protein, FKBP-13. <i>PNAS</i> 88, 6677-6681 (Aug. 1991).		1500/200-
M	CM	Itoh, N. et al. Effect of bcl-2 on Fas Antigen Mediated Cell Death. J. Immunol. 151, 621 (1993).		23200
M	CL	Itoh, N. & Nagata, S. A Novel Protein Domain Required for Apoptosis. J. B. C. 268, 10932-10937 (25 May 1993).	M	CELL
列	CK	Ishizaka-Ikeda, E. et al. Signal transduction mediated by growth hormone receptor and its chimeric molecules with the granulocyte colony-stimulating factor receptor. PNAS 90, 123-127 (1993). Itoh, N. & Nagata, S. A Novel Protein Domain Required for Apoptosis. J. B. C. 268, 10932-10937 (25 May 1993). Itoh, N. et al. Effect of bcl-2 on Fas Antigen Mediated Cell Death. J. Immunol. 151, 621-621 (1993). Jin, YJ. et al. Molecular cloning of a membrane-associated human FK506- and rapamycin-binding protein, FKBP-13. PNAS 88, 6677-6681 (Aug. 1991). Kao, P.N. et al. Nuclear target of cyclosporin A and FK506 action is specifically bound by a heterodimenic protein comprising molecular weights 90K and 45K. J. Cell. Biochem. Suppl. 0	~	
DJ	C1	Irving, B.A. & Weiss, A. The Cytoplasmic Domain of the T Cell Receptor c Chain is Sufficient to Couple to Receptor-Associated Signal Transduction Pathways. Cell 64, 891-901 (8 March 1991).		

Examiner Signature	David	Cambertson	Date Considered	11/11/03

PTO/S8/08A (10-01)
Approved for use through 10/31/2002 OMB 0651-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

tion Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number. Complete if Known Substitute for form 1449A/PTO Application Number 10/054712 INFORMATION DISCLOSURE Filing Date November 13, 2001 STATEMENT BY APPLICANT First Named Inventor Gerald R. Crabtree Art Unit 2122 1636 (use as many sheets as necessary) Examiner Name Not Yet Assigned Z Sheet 11 Attorney Docket Number APBI-P08-317 Technology Center 2100 Lee, J. et al. HER2 Cytoplasmic Domain Generates Normal Mitogenic and Transforming Signals in a Chimeric Receptor. EMBO J. 8, 167-173 (1989). CZ Lee, A. W.-m. and Neinhuis, A.W. Functional Dissection of Structural Domains in the TECH MA 2 3 2003 ED Receptor for Colony Stimulating Factor-1. J. Biol. Chem. 267, 16472-16483 (1992). Lehtola et al. Receptor Downregulation and DNA Synthesis are Modulated by EGF and TPA DA in Cells Expressing an EGF/neu Chimera. Growth Factors 1, 323-334 (1989). Lehtola et al. A chimeric EGFR/neu receptor in functional analysis of theneu oncoprotein. DB Acta Oncologia 31, 147-150 (1992). Lehvaslaiho et al. A Chimeric EGF-R-neu Proto-Oncogene Allows EGF to Regulate neu Tyrosine Kinase and Cell Transformation. EMBO J. 8, 159-166 (1989). Lehvaslaiho, H. et al. Regulation by EGF is maintained in an overexpressed chimeric DD EDG/neu receptor tyrosine kinase. J. Cell. Biochem. 42, 123-133 (1990). Letourneur, F. et al. T-cell and basophil activation through the cytoplasmic tail of T-cellreceptor zeta family proteins. PNAS 88, 8905-8909 (1991). Letourneur & Klausner. Activation of T Cells by a Tyrosine Kinase Activation Domain in the Cytoplasmic Tail of CD3 e. Science 255, 79-82 (1992). Lev et al. Receptor functions and ligand-dependent transforming potential of a chimeric kit proto-oncogene. Mol. Cell. Biol. 10, 6064-6068 (1990). Lev et al. A Specific Combination of Substrates is Involved in Signal Transduction by the kit-Encoded Receptor. EMBO J. 10, 647-654 (1991). Liu et al. Cloning, expression, and purification of human cyclophilin in Escherichia coli and assessment of the catalytic role of cysteines by site-directed mutagenesis. PNAS 87, 2304 (1990)Liu et al. Calcineurin is a Common Target of Cyclophilin-Cyclosporin A and FKBP-FK506 Complexes. Cell 66, 807 (1991). Liu et al. Inhibition of T Cell Signaling by Immunophilin-Ligand Complexes Correlates With Loss of Calcineurin Phosphatase Activity. Biochemistry 31, 3896-3901 (1992). Liu. FK506 and cyclosporin, molecular probes for studying intracellular signal transduction. Immunology Today 14, 290 (1993). Maki, N. et al. Complementary DNA encoding the human T-cell FK506-binding protein, a peptidylprolyl cis-trans isomerase distinct from cyclophilin. PNAS 87, 5440-5443 (July 1990). Mares et al. A Chimera between Platelet-Derived Growth Factor B-receptor and Fibroblast Growth Factor Receptor-1 Stimulates Pancreatic β-DNA Synthesis in the Presence of PDGF-BB. Growth Factors 6, 93-101 (1992).

Examiner Dand fumbutsor 11/11/03 Considered Signature

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PTO/SB/08A (10-01)
Approved for use through 10/31/2002.OMB 0651-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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A	DO	Margolis et al. All Autophosphorylation Sites of Epidermal Growth Factor (EGF) Receptor and HER2/neu are Located in their Carboxyl-Terminals Talls. <i>J. Biol. Chem.</i> 264, 10667-10671 (1989).		
列	DP	Mattila et al. The Actions of Cyclosporin A and FK506 Suggest A Novel Step in the Activation of T Lymphocytes. <i>EMBO J.</i> 9, 4425-4433 (1990).		
可可	DQ	Meyer et al. Synthetic Investigations of Rapamycin. 1. Synthesis of a C10-C21 Fragment. J. Org. Chem. 57, 5058-5060 (1992).		
31	DR	Michnick et al. Solution Structure of FKBP, a Rotamese Enzyme and Receptor for FK506 and Rapamycin. Science 252, 836-839 (1991).	•	200
M	DS	Moe et al. Transmembrane Signaling by a Chimera of the Escherichia coli Aspartate Receptor and the Human Insulin Receptor. PNAS 86, 5683-5687 (1989).	,	PECEIVE VER 1600/200
M	DT	Nakatsuka et al. Total Syntheses of FK506 and an FKBP Probe Reagent, (C8, C9-13C2)-FK506. J. Am. Chem. Soc. 112, 5583 (1990).	CE	1EP 32003
A	טט	Nussbaumer et al. C9-Imino and C10-Amino Derivatives of Ascomycin (21-Ethyl-FK506). Tetrahedron Letters 33, 3845-3846 (1992).		1600/2000
	DV	Orloff et al. Family of Disulphide-Linked Dimers Containing the ς and η Chains of the T-Cell Receptor and the y Chain of the Fc Receptors. <i>Nature</i> 347, 189-191 (1990).		
M	DW	Palmiter et al. Transgenic Mice. Cell 41, 343-345 (1985).		
3	DX	Patchett et al. Analogs of Cyclosporin A Modified at the D-ALA ⁸ Position. <i>J. Antibiotics</i> 45, 94-102 (1992).		
件架皮供	DY	Peles et al. Regulated Coupling of the Neu Receptor to Phosphatidylinositol. <i>J. Biol. Chem.</i> 267, 12266-12274 (1992).		
Te	DZ	Price et al. Human cyclophilin B: A second cyclophilin gene encodes a peptidyl-prolyl isomerase with a signal sequence. PNAS 88, 1903 (1991).		
A	EA	Ptashne et al. Activators and Targets. Nature 346, 329-331 (1990).		
M	EB	Ragan et al. Studies of the Immunosuppressive Agent FK506: Synthesis of an Advanced Intermediate. J. Org. Chem. 54, 4267-4268 (1989).		
De	EC	Reins et al. Anti-epidermal growth factor receptor monoclonal antibodies affecting signal transduction. J. Cell. Biol. 51, 236-248 (1993).		
DJ	ED	Riedel et al. Cytoplasmic Domains Determine Signal Specificity, Cellular Routing Characteristics and Influence Ligand Binding of Epidermal Growth Factor and Insulin Receptors. <i>EMBO J.</i> 8, 2943-2954 (1989).		
DJ	EE	Romeo et al. Cellular immunity to HIV activated by CD4 fused to T cell or Fc receptor polypeptides. <i>Cell</i> 64, 1037-1046 (1991).		

Examiner David Lambutson	Date Considered	11/11/03

PTO/SB/08A (10-01)
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Complete if Known 10/054712 Application Number INFORMATION DISCLOSURE Filing Date November 13, 2001 Gerald R. Crabtree RECEIVED STATEMENT BY APPLICANT First Named Inventor Art Unit 2122-1636 (use as many sheets as necessary) Examiner Name NOT YET ASSIGNED DALLY A APBI-P08-317 Sheet 8 of 11 Attorney Docket Number Technology Center 2100 EF Romo et al. Synthetic Investigations of Rapamycin. 2. Synthesis of a C22-C42 Fragment. J.

M	1	Org. Chem. 57, 5060-5063 (1992).		
N	EG	Romo et al. Total Synthesis of Rapamycin Using an Evans-Tischenko Fragment Coupling. <i>J. Am. Chem. Soc.</i> 115, 7906-7907 (1993).		
K	EH	Rosen et al. Inhibition of FKBP Rotamase Activity by Immunosuppressant FK506: A Twisted Amide Surrogate. Science 248, 863 (1990).		
H	EI	Romo et al. Total Synthesis of Rapamycin Using an Evans-Tischenko Fragment Coupling. <i>J. Am. Chem. Soc.</i> 115, 7906-7907 (1993). Rosen et al. Inhibition of FKBP Rotamase Activity by Immunosuppressant FK506: A Twisted Amide Surrogate. <i>Science</i> 248, 863 (1990). Rosen et al. Proton and Nitrogen Sequential Assignments and Secondary Structure Determination of the Human FK506 and Rapamycin Binding Protein. <i>Biochemistry</i> 30, 4774-4789 (1991). Rosen et al. Study of Receptor-Ligand Interactions Through Receptor Labeling and Isophedited NMR. <i>J. Org. Chem.</i> 56, 6262 (1991). Rosen et al. Natural Products as Probes of Cellular Function: Studies of Immunophilins. <i>Angew. Chemie. Int. Ed. Eng.</i> 31, 384-400 (1992). Rosen et al. Activation of an Inactive Immunophilin by Mutagenesis. <i>J. Am. Chem. Soc.</i> 115, 821-822 (1993).	3	ŠO.
A B	EJ	Rosen et al. Study of Receptor-Ligand Interactions Through Receptor Labeling and Isolate Edited NMR. J. Org. Chem. 56, 6262 (1991).	MA	EN SON
31	EK	Rosen et al. Natural Products as Probes of Cellular Function: Studies of Immunophillins. Angew. Chemie. Int. Ed. Eng. 31, 384-400 (1992).	VZ	7/000
34	EL	Rosen et al. Activation of an Inactive Immunophilin by Mutagenesis. <i>J. Am. Chem. Soc.</i> 115, 821-822 (1993).		00/2900
H	EM	Rosen, M.K. The molecular basis of receptor-ligand-receptor interactions: Studies of the Immunophilin FKBP12. Abstract of Doctoral Thesis (1993).		
A 3	EN	Roussel et al. Antibody-Induced Mitogenicity Mediated by a Chimeric CD2-c-fms Receptor. Mol. Cell. Biol. 10, 2407-2412 (1990).		
R ,	ĒΟ	Rudert et al. Apoptosis in L929 cells expressing a CD40/Fas chimeric receptor: Dissociation of stimulatory from inhibory death signaling functions. <i>Biochem. Biophys. Res. Comm.</i> 204, 1102 (1994).		
£1	EP	Sampson & Gotschlich. Neisseria meningilidis encodes an FK506-inhibitable rotamase. PNAS 89, 1164 (1992).		
A	EQ	Schreiber, S. L. Synthesis of materials with physiological properties. Abstract of NIH Grant R37GM38627, (1987).		
E G	ER	Schreiber et al. Is There a Scaffolding Domain within the Structure of the Immunosuppressive Agent Cyclosporin A (CsA)? Studies of the Cyclophilin Binding Domain of CsA. Tetrahedron Lett. 29, 6577 (1988).		
21	ES	Schreiber, S. L. Analysis of cyclosporin-receptor interaction: Synthesis of semi-peptide and non-peptide analogs of cyclosporin A. Abstract of NIH Grant P01GM406600001 (1989).		
D)	ET	Schrelber et al. Studies Relating to the Synthesis of the Immunosuppressive Agent FK506: Application of the Two Directional Chain Synthesis Strategy to the Pyranose Moiety. J. Org. Chem. 54, p. 9,15, 17 (1989).		

Examiner Signature David Sumbertson	Date Considered	11/11/03

Examiner Signature Daird Jambertson

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PTO/SB/08A (10-01)
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	EU	Schreiber et al. Protein Overproduction for Organic Chemists. Tetrahedron 47, 2543-2562		
DI		(1991).		
	EV	Schreiber et al. Immunophilin-Ligand Complexes as Probes of Intracellular Signaling		
H		Pathways. Transplantation Proceedings 23, 2839 (1991).		
9	EW	Schreiber, S. L. Chemistry and Biology of the Immunophilins and their Immunosuppressive		
H		Ligands. Science 251, 283 (1991).	74	\sim
- 0	EX	Schreiber, S. L. Synthesis of materials with physiological properties. Abstract of NIH Grant	10	
\supseteq		R37GM38627, (1992).	MAX.	,\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
DI	EY	Schreiber et al. Molecular Recognition of Immunophilins and Immunophilin-Ligand Complexes. <i>Tetrahedron</i> 48, 2545-2558 (1992).	W2.	32000
700	EZ	Schreiber et al. The Mechanism of Action of Cyclosporin A and FK506. Immunology Today	150	160
DJ	1	13, 136-142 (1992). 		000/200
H	FA	Schreiber, S. L. Immunophilin-Sensitive Phosphatase Action in Cell Signaling Pathways. <i>Cell</i> 70, 365-369-8 (1992).		CEIVE 3 2003 1800/2900
	FB	Schultz et al. Atomic Structure of the Immunophilin FKBP13-FK506 Complex: Insights Into the	-	
31		Composite Binding Surface for Calcineurin. J. Am. Chem. Soc. 116, 3129-3130 (1994).		
-	FC	Seedorf et al. Analysis of platelet-derived growth factor receptor domain function using a		
ÐŁ		novel chimeric receptor approach. J. Biol. Chem. 266, 12424-12431 (1991).		
	FD	Seedorf et al. Differential effects of carboxy-terminal sequence deletions on platelet-derived		
H		growth factor receptor signaling activities and interactions with cellular substrates. <i>Mol. Cell. Biol.</i> 12, 4347-4356 (1992).		
	FE	Selvakumaran et al. Myeloblastic leukemia cells conditionally blocked Myc-estrogen receptor		
M		chimeric transgenes for terminal differentiation coupled to growth arrest and apoptosis. <i>Blood</i> 81, 2257 (1993).		
¥_3.	FF	Serafini et al. Selection and characterization of mutants in a signal transduction/transmission		
\mathcal{M}		pathway. J. Cell. Biochem. Suppl. 0 (6 Part A), 89, Abstract #B234 (1992).		
	FG	Shaw et al. Identification of a Putative Regulator of Early T Cell Activation Genes. Science	1	
DJ		241, 202 (1988).		
<u> </u>	FH	Sistonen et al. Activation of the neu Tyrosine Kinase Induces the fos/jun Transcription Factor	-	
T/J		Complex, the Glucose Transporter, and Ornithine Decarbodylase. J. Cell. Biol. 109, 1911-1919 (1989).	İ	
A				
D.	FI	Smith et al. FKBP54, a Novel FK506 Binding Protein in Avian Progesterone Receptor Complexes and HeLa Extracts. <i>J. Biol. Chem.</i> 268, 24270-24273 (1993).		
W	FJ	Somers et al. Synthesis and Analysis of 506BD, a High Affinity Ligand to the Immunophilin, FKBP. J. Am. Chem. Soc. 113, 8045-8056 (1991).		
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PTO/SB/08A (10-01)
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##	FK	Standaert et al. Molecular cloning and overexpression of the human FK506-binding protein FKBP. Nature 346, 671 (1990).			
A	FL	Standaert, R.F. Biochemical and structural studies of the FK506- and rapamycin-binding proteins (FKBPs). Abstract of Doctoral Thesis (1992).	4	En	
R	FM	Tai et al. Association of a 59-Kilodalton Immunophilin with the Glucocorticoid Receptor Complex. Science 256, 1315-1318 (1992).	14	IN SIVE	•
A	FN	Tai et al. P59 (FK506 Binding Protein 59) Interaction with Heat Shock Proteins is Highly Conserved and May Involve Proteins Other Than Steroid Receptors. <i>Biochemistry</i> 32, 8842-8847 (1993).	CEA	ECEIVE 15 2 3 2003 159 1600/2900	(
F	FO	Tanida et al. Yeast Cyclophilin-related gene encodes a nonessential second peptidyl-prolyl cls-trans isomerase with the secretory pathway. <i>Transplantation Proceedings</i> 23, 2856 (1991).		42900	
A	FP	Traber et al. Cyclosporins – New Analogues by Precursor Directed Biosynthesis. <i>J. Antibiotics</i> 42, 591-597 (1989).			
A	FQ	Ullman et al. Site of action of cyclosporin and FK506 in the pathways of communication between the T-lymphocyte antigen receptor and the early activation genes. <i>Transplant</i> . <i>Proceed</i> . 23, 2845 (1991).			
H	FR	Van Duyne et al. Atomic Structure of the Rapamycin human immunophilin FKBP-12 complex. J. Am. Chem. Soc. 113, 7433 (1991).			
21	FS	Van Duyne et al. Atomic Structure of FKBP-FK506, an Immunophilin-Immunosuppressant Complex. Science 252, 839-842 (1991).			
DJ.	FT	Van Duyne et al. Atomic Structures of the Human Immunophilin FKBP12 Complexes with FK506- and Rapamycin. <i>J. Mol. Biol.</i> 229, 105-124 (1993).			
AL	FÜ	VanRheenen et al. An Improved Catalytic OsO4 Oxidation of the Olefins to Cis-1,2 Glycols Using Tertiary Amine Oxides as the Oxidant. <i>Tetrahedron Letters</i> 23, 1973-1976 (1976).			
A	FV	Venkitaraman et al. Interleukin 7 receptor functions by recruiting the tyrosine kinase p59 ^{tym} through a segment of its cytoplasmic tail. <i>PNAS</i> 89, 12083-12087 (1992).			
DJ	FW	Verweij et al. Cell Type Specificity and Activation Requirements for NFAT-1 (Nuclear Factor of Activated T-Cells) Transcriptional Activity Determined by a New Method Using Transgenic Mice to Assay Transcriptional Activity of an Individual Nuclear Factor. J. Biol. Chem. 265, 15788 (1990).			
奸	FX	Walsh et al. Cyclosporin A, the Cyclophilin Class of Peptidylprolyl Isomerases, and Blockade of T Cell Signal Transduction. <i>J. Biol. Chem.</i> 267, 13115 (1992).			
7	FY	Wandless et al. FK506 and Rapamycin Binding to FKBP: Common Elements Involved in Immunophilin-Ligand Complexation. J. Am. Chem. Soc. 113, 2339-2341 (1991).			

Examiner Signature David Jambertson Date Considered 11/11/03

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PTO/SB/08A (10-01)
Approved for use through 10/31/2002.OMB 0651-0031
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A	FZ	Wandless, T.J. Turning genes on and off using FKBP and FK506. Doctoral Thesis (1993).
21	GA	Watanabe-Fukunga et al. Lymphoproliferation Disorder in Mice Explained by Defects in Fas Antigen that Mediates Apoptosis. <i>Nature</i> 356, 314-317 (1992).
1	GB	Weissman et al. Molecular Cloning and Chromosomal Localization of the Human T-Cell Receptor ζ Chain: Distinction from the Molecular CD3 Complex. <i>PNAS</i> 85, 9709-9713 (1988).
4	GC	Wennstrom et al. The platelet-derived growth factor beta-receptor kinase insert confers specific signaling properties to a chimeric fibroblast growth factor receptor. <i>J. Biol. Chem.</i> 267, 13749-13756 (1992).
21	GD	Wittbrodt et al. The Xmrk Receptor Tyrosine Kinase is Activated in Xiphophorous Maligant Melanoma. EMBO J. 11, 4239-4246 (1992).
DI	GE	Yang et al. A Composite FKBP12-FK506 Surface That Contacts Calcineurin. J. Am. Chem. Soc. 115, 819-820 (1993).
M	GF	Yarden et al. Growth factor receptor tyrosine kinases. Ann. Rev. Biochem. 57, 443-478 (1988).
A	GG	Zelle et al. Systematic Degradation of Zincophorin: A Stereoselective Synthesis of the C17-C25 Fragment. <i>J. Org. Chem.</i> 51, 5032-5036 (1986).
Al	GH	Zhang et al. The insulin receptor-related receptor. J. Biol. Chem. 267, 18320-18328 (1992).
A	GI	Zydowsky et al. Active site mutants of human cyclophilin A separate peptidyl-prolyl isomerase activity from cyclosporin A binding and calcineurin inhibition. <i>Prot. Sci.</i> 1, 1092 (1992).
DI	GJ	Zydowsky et al. Overexpressoin, purification, and characterization of yeast cyclophilins A and B. <i>Protein Sci.</i> 1, 961 (1992).

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